

**POST-REIMBURSEMENT
FOLLOW-UP STUDY OF THE
PRECISION® IMPLANTABLE
AND NEUROSTIMULATOR
PRECISION®**

STATISTICAL ANALYSIS PLAN

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LIST OF ABBREVIATIONS

NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
CNEDIMTS	National Commission for the Evaluation of Medical Devices and Health Technologies
HAD	Hospital Anxiety and Depression scale

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SUMMARY OF THE STUDY

1. Title of the study	Post-reimbursement follow-up study of the implantable and rechargeable, neurostimulator PRECISION®.
2. Number - version date of the protocol	Version 10.2 - June 07, 2013
3. Sponsor	CEMKA-EVAL
4. Origin	Study carried out at the request of the High Authority of Health.
5. Centers / Investigators	All centers using the device over the inclusion period. These centers will be described for the criteria of geographical location, public or private status, volume of activity and specialities of the investigators. Doctors in these centers (neurosurgeons or anaesthetists).
6. Population / Treatment studied	All patients implanted (primary implantation and renewal) with the PRECISION® neurostimulator during the inclusion period (1 year).
7. Objectives of the project	Evaluate the long-term effectiveness, complications, revision and final explant rates of the devices.
8. Evaluation criteria	<p>Main Criterion : Percentage of patients with at least a 50% improvement in mean overall pain over the past 8 days, assessed by numerical scale, at the first follow-up visit, at 1 year and 2 years.</p> <p>Secondary criteria :</p> <ul style="list-style-type: none"> • Percentage of patients with an improvement of at least 30% in mean overall pain over the past 8 days, assessed by numerical scale • Patients' opinions on the evolution of pain • Evolution of consumption of other pain treatments (drugs and other therapies) • Evolution of the impact on activities of daily living • Evolution of quality of life (SF12), anxiety and depression (HAD questionnaire) • Explanation, reoperation or device change rate • Complications rate
9. Experimental design	<p><u>Methodology</u>: Prospective observational study with a 2-year follow-up</p> <p><u>Investigator Recruitment</u>: Selected centers will be notified by mail. An Implant during on-site visits will be organized.</p> <p><u>Patient recruitment</u>: During the inclusion period, the investigating centers should offer to participate in the study to all patients who have a spinal cord stimulator implant.</p>
10. Sample size	<p>Comprehensive study: the number of patients expected is estimated at about 100 patients over one year, corresponding to about 70 primary and 30 secondary patients.</p> <p>With a loss of sight rate of < 20%, this number makes it possible to estimate the main judgment criterion with an accuracy of $\pm 12\%$.</p>

11. Eligibility criteria	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Adult patient with a PRECISION® neurostimulator implanted in the spinal cord as a primary implant or in the renewal of their stimulator. <p><u>Criteria for non-inclusion:</u></p> <ul style="list-style-type: none"> • Patient Refusal • Patient whose long-term follow-up will not be possible
12. Statistical method	<p>Statistical analyses will be carried out each year on the data collected.</p> <p>Data management and statistical analysis will be performed using SAS® software (North Carolina, USA). The descriptive analysis of qualitative and ordinal variables will include the number and frequency of each modality with its 95% confidence interval. The quantitative variables will include the mean, standard deviation and their confidence interval as well as the median and extreme values.</p> <p>For longitudinal analyses, survival analysis and mixed model analyses will take into account the follow-up time of each patient, the number of people lost to follow-up and missing data.</p>
13. Data collected	<ul style="list-style-type: none"> • <u>Inclusion data</u>: socio-demographic data (age, sex), indication of spinal cord stimulation, pain intensity and location, previous pain treatments, history), implantation data, early complications. • <u>Follow-up data</u> (follow-up at 1-3 months, 6 months, 1 year, 2 years): pain intensity (on a numerical scale), changes in drug use, complications, explant, revision. • <u>Patient data (self-administered)</u>: patient satisfaction, adverse events.

1. CONTEXT AND JUSTIFICATION OF THE STUDY

1.1 SPINAL CORD STIMULATION FOR ANALGESIC PURPOSES

Medullary neurostimulation for analgesic purposes is a therapy developed over the past forty years. It is considered an effective (i-ii- -iii- -iv) alternative to repeated back surgery, drugs or other therapies, without causing damage to the nervous system: the complications related to the constituent materials of the components are few and generally benign.

The indications for spinal cord neurostimulation are as follows:

- irreducible chronic neuropathic pain, after failure of other therapeutic means, secondary to:
 - chronic radiculalgia (sciatica, cruralgia, cervico-brachialgia)
 - peripheral nerve damage, post-traumatic or post-surgical nerve damage
 - amputation (algo-hallucinoses)
 - a complex regional painful pain syndrome (sympathetic reflex dystrophies, peripheral causalgia)
- peripheral ischemic pain such as stage III, IV arteritis

Other therapeutic methods that should have previously been used include level I and II analgesics, physiotherapy, physiotherapy, muscle relaxants, nerve block anaesthesia, antiepileptics, tricyclic antidepressants, transcutaneous neurostimulation coupled with physiotherapy and behavioural approach and, in the case of Burger's disease, prostacyclin.

1.2 THE PRECISION® NEUROSTIMULATOR

Boston Scientific manufactures and markets in France an implantable and rechargeable spinal cord neurostimulator, PRECISION®. This device has been the subject of two publications on non-comparative studies, respectively on 49 implanted patients (IDE study) (v) and 12 patients not eligible according to IDE study criteria and implanted (vi).

The PRECISION® neurostimulator was the subject of a CEPP notice dated May 26, 2009 and a 3-year registration on the List of Products and Services (Order of February 2, 2010, published in the Official Journal of February 10, 2010).

1.2.1 Indications retained by the CNEDIMTS

As a rechargeable neurostimulator, PRECISION® is indicated for patients with

- general indications for spinal cord neurostimulation
- and
- requiring a high level of stimulation, resulting in:
 - a lifetime of less than 30 months after the first implantation of a non-rechargeable implantable spinal cord neurostimulator
 - or a stimulation threshold greater than 3.5 volts or 4.7 mA at the end of the test stimulation phase in naïve patients.

1.2.2 Terms of use and prescription

This system requires multidisciplinary medical care:

- In the context of a chronic pain management structure, for the validation of the indication, the evaluation of the results of the test stimulation and post-implantation follow-up;
- Implant of the system by a different person, trained in this type of action.

Long-term follow-up within the chronic pain management structure should be carried out to allow adaptation of stimulation parameters, drug treatments and to verify the achievement of pain reduction objectives.

The validation of the indication implies:

- An assessment of the various bio-psycho-social factors that may influence the patient's condition and may justify exclusion,
- The patient's adherence to the objectives of the treatment,
- Controls of the organic conditions allowing the installation of the device, in particular the satisfactory integrity of the posterior cords (Satisfactory Somesthetic Evoked Potentials),
- The performance of an epidural stimulation test prior to final implantation, for a minimum duration of 10 days with a desired "return home", with outpatient medical care for patients. The improvement in pain must be at least 50%.

In the CEPP opinion, the target population is estimated at between 82 and 165 patients per year.

1.3 CONDITIONS FOR RENEWAL OF REGISTRATION ON THE LIST OF PRODUCTS AND SERVICES

The commission asked the manufacturer to set up "a register analysing all implanted patients, including long-term effectiveness, complications, revision and final explant rates of the system".

The results of this study should be submitted to CEPP for review once a year. Renewal will be subject to the submission of the full results of the study.

In response to CEPP's request, Boston Scientific asked Cemka-Eval to set up an observatory for the first year of use of the device, with a 2-year follow-up of implanted patients.

2 DESCRIPTION OF THE STUDY

This was a prospective study with a follow-up of patients for 2 years.

The inclusion data included a minimum of retrospective data to describe the implanted patients, including a pre-phase test/pre-implantation questionnaire to determine, among other things, the usual level of pain over the past 8 days in naïve patients (to meet the primary objective) and pain characteristics. Information was also collected on the characteristics of the implanted devices and the stimulation parameters of analgesic neurostimulators, as well as the type of implantation performed: primary implantation or stimulator renewal.

Follow-up questionnaires were to be completed at 1 to 3 months, 6 months, 1 year and 2 years. They were completed during visits as part of the usual patient follow-up.

At each planned or additional visit, a complication sheet was completed in the event that an event related or potentially related to the implantation of the device occurred, with the consequences or consequences of this complication. The information in this form did not exempt the center from making the declaration of material vigilance with the appropriate Cerfa form.

2.1 Selection of centers

The study covered all centers implanting PRECISION® neurostimulators in France. If new centers implanted PRECISION® devices during the inclusion period, they were included as they were introduced.

2.2 Patient eligibility criteria

Inclusion criteria

- All patients 18 years of age or older implanted with a PRECISION® neurostimulator during the inclusion period, including:
 - Naïve patients (first implantation);
 - Patients previously implanted with a spinal cord stimulator, regardless of brand, and benefiting from the reimplantation of a PRECISION® neurostimulator (reimplantation).
- Patients who have read the newsletter and given their written consent.

For naïve patients, the inclusion date will be the date of final implantation of the neurostimulator.

The inclusion period is set at 1 year. However, the Scientific Committee reserves the right to extend the inclusion period to include 100 first-time implant patients.

Exclusion criteria

- Patient Refusal
- Patient whose regular follow-up is difficult (patients living abroad and coming to France only for implantation)

For all these patients, the investigator completed a non-inclusion register containing only the date of implantation of the PRECISION® neurostimulator and the reasons for non-inclusion.

2.3 Data collection

The data collected were of two kinds: data on pain characteristics and medical data. These were collected by the doctor via an observation booklet composed of:

- implant sheet,

- follow-up questionnaires identical to 1-3 months, 6 months, 1 year and 2 years,
- complication sheets, which could be completed at any time during follow-up if a complication occurred and several times for the same patient, if necessary.

If the patient had not been seen in consultation during the 1st year or during the 2nd year, the CRA responsible for follow-up of the study would call the patient or his or her treating physician to collect news about at least the vital status and maintenance of the device.

The doctor had to send the completed forms to Cemka-Eval by T envelope. He kept the original of the questionnaire in a patient follow-up binder.

In addition, patients were required to complete a self-administered questionnaire at each visit, including the pre-testing/pre-implantation phase for naïve patients and give it to the doctor who sent it back to Cemka-Eval using a T envelope.

3 OBJECTIVES OF THE STUDY

In accordance with the request of the CNEDIMTS, the objectives of this study are to evaluate the long-term efficacy, complications, revision and explant rates of the Boston Scientific rechargeable neurostimulator, PRECISION®.

4 ANALYSIS VARIABLES

4.1 Definition of evaluation criteria

4.1.1 Main evaluation criteria

The study of effectiveness in real practice will be based primarily on the **primary endpoint**, which is the percentage of patients improved by at least 50% on the numerical scale between the pre-implantation period and the measurements made during follow-up.

This criterion will be assessed at the 1st follow-up visit, at 1 and 2 years. However, it can only be evaluated in primary implanted patients.

To be as compatible as possible with the practice of collecting pain information in the centers concerned, it was decided to use a measure of the average overall pain over the last 8 days without distinction of location, using a numerical scale.

4.1.2 Secondary evaluation criteria

Pain measurements will also include questions on the level of pain present at the time of measurement and the level of the most intense pain over the past 8 days. These criteria will be used as secondary criteria.

Other **secondary evaluation criteria** were collected (or calculated) and will be analyzed:

- Percentage of patients improved by at least 30% on the numerical scale (ECH) between the pre-implantation period and measurements made during follow-up, this criterion can be considered satisfactory and associated with a decrease in other treatments for some patients with neuropathic pain;
- Patients' views on pain relief;
- Evolution of the consumption of other pain treatments (drugs and other therapies);
- Evolution of the impact on activities of daily living, return to employment for working-age patients.
- Evolution of quality of life (measured on SF12), evolution of anxiety and depression measured on the HAD (Hospital Anxiety and Depression Scale) questionnaire.

Complication, revision and final explant rates will be calculated at each follow-up point based on the data available for the patients being monitored. The nature of the complications will be described in detail for each patient.

4.2 Data collected

The data collected are collected through a non-inclusion register, an inclusion medical questionnaire, 4 follow-up medical questionnaires (1-3 months, 6 months, 1 year and 2 years), 5 patient self-questionnaires (1 per visit) and complication sheets.

4.2.1 Non-inclusion register

The data collected in the non-inclusion register were as follows:

- Age and sex of the patient
- Date of implant and indication
- Reason for non-inclusion

4.2.2 Medical Inclusion Questionnaire

The data collected in the medical inclusion questionnaire were as follows:

- Sociodemographic data: year of birth, sex, professional activity (type, in activity, work stoppage, work accident, dispute);
- Characteristics of the pathology: seniority, significant history (surgical procedures, trauma), indications, pain topography, pain intensity, pain characteristics described by the DN4 questionnaire (vii) ;
- Consumption of analgesic treatments (drugs and other therapies);
- Impact on activities of daily living;
- Quality of life (SF12);
- Type of stimulator replaced and/or implanted and electrodes used; test before implantation;
- Parameters of the most effective stimulation (number of electrodes, number of active pads, pulse width, intensity, frequency, number of zones, material description)

The first page of the observation booklet included the patient's date and place of birth, as well as his telephone number and contact details of the patient's attending physician. These data were not entered and were only used if the patient was lost to follow-up before the end of the study.

4.2.3 Follow-up medical questionnaires

The data collected in the follow-up medical questionnaires were as follows:

- Professional situation, in order to document the returns to employment;
- Parameters of the most effective stimulation;
- Possible withdrawal of the stimulator and reason for withdrawal
- Complications, if any, including explants or repositionings;

For patients who have not been seen, the investigating physicians will be responsible for contacting the physician or family again to collect some of the information;

4.2.4 Patient self-questionnaire

The data collected in the patient quality of life self-administered questionnaire were as follows:

- BPI (Brain Brief Pain Inventory) Questionnaire;
- Pain intensity (on the numerical scale);
- Patients' opinions on the evolution of pain
- Consumption of analgesic treatments (drugs and other therapies) and changes in relation to pre-implantation consumption;
- Impact on activities of daily living (concise pain questionnaire);
- Quality of life (SF12);
- HAD (Hospital Anxiety Depression Scale) Questionnaire;

4.2.5 Complication sheet

The data collected in the complication sheets were as follows:

- Type of complication: electrode displacement/migration, stimulator migration, electrode fracture, extension fracture, connector problem, skin erosion (healing phase or remote), epidural hematoma, infection, undesirable stimulation, allergy, exhausted battery, loss of efficiency and death...
- Hospitalizations or hospitalization extensions related to complications;
- Corrective actions to be taken following complications such as: electrode or extension change, electrode repositioning, stimulator pocket revision, stimulator change, stimulator reprogramming (in case of loss of efficiency), explant.

4.3 Derived variables

4.3.1 Medical questionnaire

Several derived variables will be created from the questions and data collected in the medical questionnaire. These variables are presented in the table below.

The classes of the derived variables will be validated during the data review according to the distributions actually observed.

Table 1: List of derived variables from the medical inclusion questionnaire

Name of the Table	Variable name	Description	Calculation method / terminals used
Included_med	age	Patient's age at inclusion	Year of completion of the questionnaire - year of birth of the patient Mean (standard deviation, min/max) Median
Included_med	Age_cl	Patient's age at inclusion - Age classes	1-[18-30[years 2-[30-60[years 3- ≥ 60 years old
Included_med	Delay_imp_prec	For reimplanted patients, delay between inclusion and previous implantation	Implant date - date of 1st Implant

4.3.2 Follow-up medical questionnaire and self-administered patient questionnaire

Several derived variables will be created from the questions and data collected in each follow-up medical questionnaire. These variables are presented in the table below.

Table 2: List of derived variables from the follow-up medical questionnaire

Name of the Table	Variable name	Description	Calculation method / terminals used
Follow-up_med	Delay_monitoring_imp	Time from follow-up visit to inclusion	Date of completion of the follow-up questionnaire - date of Implant
Follow-up_pat	Delay_monitoring_imp	Time from follow-up visit to inclusion	Date of completion of the self-monitoring questionnaire - date of Implant

4.3.3 Complication sheet

For each patient listed in the complication sheets, several derived variables will be constructed. These variables are presented in the table below.

Table 3: List of derived variables from the register

Variable name	Description	Calculation method / terminals used
Delai_comp_imp	Delay between the onset of the complication and inclusion	Date of complication - date of Implant
Delay_dc_imp	Time from death to inclusion	Date of death - date of Implant
Comp_duration	Duration of the complication	End date of the event - date of occurrence of the complication

5 RECODED VARIABLES

The following free-to-air variables will be recoded before analysis:

Questionnaire	Variable
Non-inclusion register	"Other" indication
Medical Inclusion Questionnaire	"Other" indication
Medical Inclusion Questionnaire	Reason for not performing the test
Medical Inclusion Questionnaire	Type of electrodes
Medical Inclusion Questionnaire	Previous material (for reimplanted patients)
Medical Inclusion Questionnaire	Model / Model no. / Manufacturer
Medical Inclusion Questionnaire	Most effective stimulation: vertebral level
Follow-up medical questionnaires	"Other" reason for withdrawal from the neurostimulator
Follow-up medical questionnaires	"Other information" if patient not seen within the year
Patient self-questionnaires	Name of the drug: recoding to INN and classification to : <ul style="list-style-type: none"> • NSAIDS • Level 1 analgesics • Level 2 analgesics • Level 3 analgesics • Anti-epileptic • Antidepressant
Patient self-questionnaires	Dosage for one capsule / tablet or other
Patient self-questionnaires	Number of capsules/capsules or tablets or other per day
Complication sheets	"Other" complication

Complication sheets	Cause of death
Complication sheets	"Other" medical or surgical intervention
Complication sheets	<p>A complication will be considered serious if the complication has induced:</p> <ul style="list-style-type: none"> • A permanent handicap • A hospitalization • An extension of hospitalization • A new medical or surgical procedure • A Death

6 SAMPLE CALCULATION AND POWER

6.1 Number of patients required

This was a comprehensive one-year study. The PRECISION® neurostimulator had not been on the market for long at the time of the study's launch and was still in a period of increasing load. The number of patients implanted in 2013 was estimated at 100 patients.

With regard to the main endpoint, which is the percentage of patients whose pain is improved by at least 50% (in primary implants), this percentage will be estimated with an accuracy of $\pm 12\%$, with the assumption of a percentage of 70% of primary implants in the cohort and the most negative assumption (in terms of accuracy) of 50% of improved patients

6.2 Number of centers

As this device was newly marketed at the time of the study's Implant, the number of centers performing the activity of placing PRECISION® neurostimulators for analgesic purposes was still in the ascending phase. According to information provided by Boston Scientific, there were approximately 15 centers in 2012.

New centers establishing during the inclusion period were also solicited.

7 POPULATIONS OF ANALYSIS

7.1 Patient population

The study population consists of all patients implanted (primary or re-implanted) with a Precision® neurostimulator.

All data from all patients included in the study will be analyzed.

The efficacy analysis will be performed on primary implanted patients.

Statistical analyses will be carried out with a risk threshold of $\alpha = 5\%$ bilateral.

All linear models will be adjusted by status (public/private) and activity level of the center, inclusion value of the dependent variable and other variables of interest.

The patient groups considered for analysis are:

- All patients (EP): all patients included in the study. This group of patients is considered for socio-demographic and safety analyses.
- Efficacy analysis set - per protocol (EE): all primary implanted patients.

7.2 Physician population

The population of investigators who agreed to participate in the study will be analyzed in 2 subgroups:

- "Active" investigators, who have included at least 1 patient in the registry or study and whose data are usable;
- Inactive" investigators who did not include any patients in the study or registry.

Participating centers will be described according to the following characteristics: public/private status, level of activity, specialty of physicians practicing implantations, method of implantation.

8 STATISTICAL ANALYSIS

The statistical analyses will cover all patients selected in the study and whose data collected will be reported as usable during the data review.

The statistical analyses carried out will be descriptive univariate or based on cross-references of variables.

8.1 General methodology

8.1.1 Adjustments

Participating centers will be compared to all centers using the Precision system on the following characteristics: public/private status, level of activity, specialty of physicians practicing implants, implantation method.

If it appears that participating centers differ significantly from all centers in any of these characteristics, a comparison of patient outcomes will be made based on the characteristic that the centers differ.

If it appears that patients differ according to the characteristics of the centers, it will be necessary to adjust the results.

8.1.2 Bias

Biases in physician recruitment:

The practices of investigators who agreed to participate in the study may differ from those of non-participating investigators who implemented Precision during the inclusion period. This potential bias is unavoidable in this type of study and difficult to assess in terms of its impact on the representativeness of the patient sample. However, it can be assumed that the physicians "interested" in the study are preferably those who manage a larger number of patients corresponding to the target population. To assess this bias, the representativeness of the physicians participating in the study on the number of Precision® stimulators purchased per year will be assessed.

Patient selection bias in the registry

To limit the bias in patient selection by neurologists, a non-inclusion registry has been set up. The investigating neurologist must record in this registry all patients who received a Precision® neurostimulator, seen in consultation during the inclusion period and not included in the study.

Patient selection bias

Given the presence of the non-inclusion registry, the risk of patient selection bias is therefore limited. To ensure that patients are not selected, the following points will still be considered and discussed during the data review:

- All primary implanted patients who have not completed the pre-test self-test questionnaire will be excluded from the analyses of the primary endpoint.

8.1.3 Statistical analyses

Data management and statistical analysis will be performed using SAS® V9.3 software (North Carolina, USA).

8.1.3.1 *Presentation of the results*

- The quantitative variables will be described for each group and for the population as a whole, using the following descriptive statistics: size, number of missing values, mean, standard deviation, median, minimum and maximum.
- The qualitative variables will be described for each group and for the population as a whole using the following descriptive statistics: the number of people, the number of missing values and the percentage of each modality calculated on the responses expressed.

The 95% confidence intervals will be calculated for the main criteria and when their estimation is deemed necessary.

The probability values of the statistical tests performed will be presented in association with the corresponding statistics. Graphs may also be produced to facilitate the interpretation of the results.

8.1.3.2 *Univariate comparative analyses*

Univariate comparative analyses are not planned for this study.

8.1.3.3 *Multivariate analyses*

Multivariate analyses are not planned for this study.

8.1.3.4 *Principal component analysis (PCA)*

There are no plans to carry out an PCA for this study.

8.1.4 Missing data

Statistical analyses will be carried out on the basis of the data expressed for each of the variables.

The return to the investigating physicians for additional requests (queries) and the final review of the data will limit the missing data. However, missing data will persist.

Depending on the number of missing data remaining, the total number of patients considered may differ from one analysis to another (e.g., cross-analysis by occupational status with x missing data on occupational status and cross-analysis by current family status with y missing data on current family status) and may not necessarily equal the number of patients selected (patient population reported as "analyzable").

No imputation of missing data is expected on the study variables, with the exception of missing data on dates. For these variables, when the day is missing or not available, the value 15 will be assigned, and when the month is missing or not available, the value 6 will be assigned. This is in order to calculate the durations provided for in § 4.3 Derived variables.

8.1.5 Outliers

A systematic search for outliers for all digital data in the register and medical questionnaire will be carried out. This search for outliers will include the following variables:

- Variables from the medical inclusion questionnaire
 - Year of birth < 1912
 - Width (μ s) > 1000 or < 10
 - Normal values from 10 to 1000 μ s, steps of 10
 - Frequency (Hz) > 1200 or < 10
 - Normal values: from 10 to 1200, steps of 10 Hz
 - Intensity (mA) > 20 or < 0
 - Normal values 0 to 20, steps of 0.1 mA
- Variables of the follow-up medical questionnaire
 - Width (μ s) > 1000 or < 10
 - Normal values from 10 to 1000 μ s, steps of 10
 - Frequency (Hz) > 1200 or < 10
 - Normal values: from 10 to 1200, steps of 10 Hz
 -
 - Intensity (mA) > 20 or < 0
 - Normal values 0 to 20, steps of 0.1 mA

The list of outliers will be presented during the data review and the Scientific Committee will decide on the treatment to be applied for each of them: data to be put in missing data, data to be capped at a certain threshold. These corrections will be integrated into the database before the database freeze.

8.2 Descriptive analyses

8.2.1 Description of the participating physician population

The description of the investigator centers will cover the following parameters:

- Number of Precision neurostimulators sold / year in 2013 and 2014
- Implant method
- Public/private activity
- Speciality of the center :
 - Neurosurgery
 - Pain Center
 - Anesthesia
 - Orthopaedics

8.2.2 Description of the population of the non-inclusion register

A descriptive analysis of all patients not included will be performed.

8.2.3 Description of the patient population included

8.2.3.1 Calculations of efficiency variables

Intensity of pain:

ECH

Pain will be assessed using the 11-point ECH with 0 for no pain and 10 for maximum pain imaginable.

The following three ECH will be analyzed:

- Pain at the present time
- Usual pain for the last 8 days: main objective
- Most intense pain in the last 8 days.

Calculation of the reduction in pain intensity and percentage of responders:

The variable on which the main evaluation criterion will be based will be calculated as follows:

The relative difference in the evolution of pain intensity at a follow-up visit compared to the inclusion value is calculated as follows:

$$\Delta \text{ follow - up} = \frac{100 \times (ECH_{bs} - ECH_{sv})}{ECH_{bs}}$$

The ECH_{bs} is the value of the visual analogue scale collected at inclusion and the ECH_{sv} is the value of the ECH measured at the closest visit of 1-3 months, 6 months, 1 and 2 years of post-implantation follow-up.

A second dichotomous variable with a value of 0 or 1 is created as follows:

$$p = \begin{cases} 1 & \text{if } \Delta \text{ follow - up} > 50\% \text{ (an improvement of more 50\%)} \\ 0 & \text{if } \Delta \text{ followw - up} < 50\% \text{ (an improvement of less 50\%)} \end{cases}$$

The percentage of patients with a decrease of at least 50% in pain intensity compared to the inclusion value is the percentage of p equal to 1.

The proportions of patients with improved ECH will also be assessed for the Δ follow – up:
<10%, [10%, 30%[, [30%, 50%[, [50%, 70%[and $\geq 70\%$.

Improvement in activities of daily living:

The discomfort caused by pain on activities of daily living will be assessed using an 11-point scale with 0 for no discomfort and 10 for maximum discomfort.

The following 6 scales will be analyzed:

1. Mood
2. Ability to walk
3. Usual work
4. Relationships with others
5. Sleep
6. Taste of life.

Calculation of the reduction in discomfort and the percentage of responders:

The variable on which the main evaluation criterion will be based will be calculated as follows:

The relative difference in the evolution of the discomfort at a follow-up visit compared to the inclusion value is calculated as follows:

$$\Delta \text{ follow - up} = \frac{100 \times (\text{ECH}_{\text{bs}} - \text{ECH}_{\text{sv}})}{\text{ECH}_{\text{bs}}}$$

ECH_{bs} is the value of the discomfort collected at inclusion and ECH_{sv} is the value of the discomfort measured at the nearest visit of 1-3 months, 6 months, 1 and 2 years of post-implantation follow-up.

A second dichotomous variable with a value of 0 or 1 is created as follows:

$$p = \begin{cases} 1 & \text{if } \Delta \text{ follow - up} \geq 50\% \text{ (an amelioration more than 50\%)} \\ 0 & \text{if } \Delta \text{ follow - up} < 50\% \text{ (an amelioration less than 50\%)} \end{cases}$$

The percentage of patients with a decrease of at least 50% in discomfort compared to the inclusion value is the percentage of p equal to 1.

The proportions of patients with improved ECH will also be assessed for the Δ follow – up: <10%, [10%, 30%[, [30%, 50%[, [50%, 70%[and $\geq 70\%$.

Improving quality of life (SF-12):

The impact on quality of life will be assessed during follow-up visits using the SF-12 questionnaire.

The SF12 provides two scores: a mental and social quality of life score and a physical quality of life score

The evolution of the physical and moral scores will be calculated for each follow-up (1-3 months, 6 months, 1 year and 2 years) by calculating the difference between the baseline score and the score at the 4 follow-up visits.

The following proportions of patients will also be calculated:

- Proportion of patients with a decrease in scores (decrease in quality of life)
- Proportion of patients with increased scores (improved quality of life)

Depression scale:

The evolution of the "anxiety" and "depression" scores will be calculated for each follow-up (1-3 months, 6 months, 1 year and 2 years) by calculating the difference between the baseline score and the score at each of the 4 follow-up visits.

The following proportions of patients will also be calculated for each follow-up visit:

- Proportion of patients with a decrease in scores (improvement of symptoms)
- Proportion of patients with increased scores (decrease in symptoms)

Professional situation:

The patient's employment situation will be assessed at the inclusion visit and during follow-up visits by asking the patient if he or she is "In active employment", "On sick leave", "On disability", "Retired" or "Unemployed".

The percentage of fully active patients at a given visit will be calculated by dividing the number of "Active" patients who are not "on sick leave" by the number of "Active" patients for the visit.

For each follow-up visit, the percentage of patients returning to work will be calculated by dividing:

1. the number of "Active and sick leave" patients at the inclusion visit who are no longer "sick leave" at a given follow-up visit (numerator)
2. by the number of "Active and sick leave" patients at the inclusion visit and for whom information is available at the follow-up visit considered (denominator).

For each follow-up visit, the percentage of patients who stop working due to illness or disability will be calculated by dividing

1. the number of "Inactive - not on sick leave" patients at the inclusion visit who are "on sick leave" or "on disability" at a given follow-up visit (numerator)
2. by the number of "Inactive - not on sick leave" patients at the inclusion visit and for whom information is available at the follow-up visit considered (denominator).

Consumption of pain treatments:

The consumption of pain relief treatments will be assessed during the inclusion visit and during follow-up visits for the following treatments: Level 1 analgesics, Level 2 analgesics, Level 3 analgesics, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Antiepileptics, Antidepressants, Rehabilitation, Psychotherapy, Acupuncture, Relaxation, Hypnotherapy and Transcutaneous Stimulation.

The percentage of patients concerned by a given treatment at a visit will be calculated by calculating the ratio between:

1. the number of patients who answered "Yes" for this treatment and ;
2. the number of patients who answered the treatment question.

Patient satisfaction during follow-up

The evolution of patient satisfaction will be estimated from the self-administered follow-up questionnaires. The following data will be described:

- Proportion of patients using the continuous stimulator / Proportion of patients using the discontinuous stimulator and not at night
- Evolution of pain relief from what the patient was feeling before the implantation:
 Δ follow – up
- Proportion of patients who would be willing to restart treatment

8.2.3.2 Data and safety variables

The analysis of the safety data will be based on the following data:

- All complications related to the medical device, if any, including explants or repositionings observed since the patient's inclusion.
- All serious complications related to the medical device. A complication will be considered serious if it has induced:
 - A permanent handicap
 - A hospitalization
 - An extension of hospitalization
 - A new medical or surgical procedure
 - A Death
- Death.
 - Implant-related/non-Implant-related
 - Linked to the Precision system / not linked to the Precision system
 - Other causes (medical or surgical)
 - Unknown cause

Incidence of complications related to the device

All complications related to the medical device, including explants or repositioning, if any, that occurred during the study will be collected in the complication sheets.

The annual incidence of complications will be calculated by relating the number of complications to the duration of patient follow-up (duration of exposure): The duration of exposure to stimulation will be calculated only for patient PE, in years as follows:

$$\text{Exposure time} = (\text{end date of treatment} - \text{Implant date} + 1) / 365$$

The end date of treatment corresponds to the final explant date or the date of the last news if the patient has not been explanted

Incidence of spinal cord device revisions

The Proportion of revision of neurostimulators and/or extensions and/or electrodes that occurred during the study is collected in the complication sheets.

The annual incidence of revisions will be calculated by relating the number of revisions to the total duration of patient follow-up (exposure duration).

Impact of definitive explant of spinal cord devices

A definitive explant is defined as the permanent removal of the neurostimulator or accessories. Explanations of neurostimulators and/or extensions and/or electrodes that occurred during the study are collected in the complication sheets.

The annual incidence of explant will be calculated by relating the number of explants to the total duration of patient follow-up (duration of exposure).

8.2.4 Main analyses

The main efficacy objective is to assess the percentage of patients with at least a 50% improvement in the predominant pain measured by ECH during follow-up.

- 1) The proportion of responder.

The 95% confidence interval of this proportion will be calculated.

- 2) The proportions of patients with improved ECH will also be assessed for the Δ follow – up:
<10%, [10%, 30%[, [30%, 50%[, [50%, 70%[and $\geq 70\%$.

The 95% confidence intervals of these proportions will be calculated.

- 3) Evolution: A trend analysis will also be carried out on the ECH results at the different times of this examination. Follow-up questionnaires require that the ECH be informed at each follow-up visit. However, these visits are carried out at varying times from one patient to another and for the same patient. This analysis will therefore be carried out taking into account the repeated measurement of the different ECHs for the same patient with a mixed model.

The variable explained will be the ECH and the explanatory variable will be the time between the date of the ECH at inclusion and the dates of successive measurements of the ECH at follow-up. This analysis will take into account the fact that these ECHs are repeated data for each patient. All available observations will thus be used in the analysis, regardless of the number of ECHs per patient. In order to study the form of the relationship between ECH and delay since treatment initiation and to allow this relationship to be non-linear, a spline regression model will be used in a mixed generalized additive model.

8.2.5 Secondary analyses - efficacy

Evaluate drug consumption (drug consumption: Level 1 analgesics, level 2 analgesics, level 3 analgesics, NSAIDs, antiepileptics, antidepressants):

The proportions of subjects treated at inclusion, 1-3 months, 6 months, 1 year and 2 years after implantation will be reported with the corresponding confidence intervals.

The proportions at 1-3 months, 6 months, 1 year and 2 years after implantation will be compared to the same proportion at inclusion, shortly before implantation by the McNemar test as the data are matched.

Other treatments (rehabilitation, psychotherapy, acupuncture, relaxation, transcutaneous stimulation):

The proportions of subjects treated at inclusion, 1-3 months, 6 months, 1 year and 2 years after implantation will be reported with the corresponding confidence intervals.

The proportions at 1-3 months, 6 months, 1 year and 2 years after implantation will be compared to the same proportion at inclusion, shortly before implantation by the McNemar test as the data are matched.

Depression scale:

The following proportions of patients will be calculated and presented with their confidence interval:

- Proportion of patients with a decrease in scores (improvement of symptoms)
- Proportion of patients with increased scores (decrease in symptoms).

Impact on quality of life (SF12):

The following proportions of patients will also be calculated with their corresponding confidence interval:

- Proportion of patients with a decrease in scores (decrease in quality of life)
- Proportion of patients with increased scores (improved quality of life)

Patient satisfaction with the treatment:

The percentage of patients ready to start treatment again at 1-3 months, 6 months, 1 year and 2 years after implantation will be reported with their corresponding confidence interval.

Professional situation / Return to employment:

- 1) The proportions of all categories will be calculated and presented with their confidence intervals.
- 2) The percentage of "working" patients who are not "on sick leave" at inclusion, one year and two years after implantation will be reported with the corresponding confidence interval.

The proportions at 1-3 months, 6 months, 1 year and 2 years after implantation will be compared to the same proportion at inclusion after implantation by the McNemar test as the data are matched.

- 3) The percentage of "working" patients who are no longer "on sick leave" at one year and two years after implantation will be reported with the corresponding confidence interval.
- 4) The percentage of "working" patients who are "on sick leave" or "on disability" at one year and two years after implantation will be reported with the corresponding confidence interval.
- 5) A survival analysis will be carried out using Kaplan Meier's method for returning to work.

Improvement in activities of daily living:

- 1) The proportion of responders.
The 95% confidence interval of this proportion will be calculated.
- 2) The proportions of patients with a 50% different improvement for each item at different follow-up times will also be assessed with the following classes: <10%, [10%, 30%[, [30%, 50%[, [50%, 70%[and $\geq 70\%$
The 95% confidence intervals of these proportions will be calculated.

The evolution of the quantitative variables will also be evaluated by performing a trend analysis at the different measurement times. The variable explained will be the annoyance scale and the explanatory variable will be the time between the date of completion of the self-questionnaire at inclusion and the dates of successive measurements of the annoyance scales at follow-up. This analysis will take into account the fact that these scales are repeated data for each patient. All available observations will thus be used in the analysis, regardless of the number of scales per item per patient. In order to study the form of the relationship between each scale and time since treatment was introduced and to allow this relationship to be non-linear, a spline regression model will be used in a mixed generalized additive model.

Patient satisfaction during follow-up

The evolution of patient satisfaction will be estimated from the self-administered follow-up questionnaires. The following data will be described:

- Proportion of patients using the continuous stimulator / proportion of patients using the discontinuous stimulator
- Evolution of pain relief from what the patient was feeling before the implantation
- Evolution of pain relief compared to the previous visit

8.2.6 Secondary analyses - safety

Evaluate the rate of complications related to the medical device.

- 1) The number of complications and the number of patients with device related complications, as well as the number of deaths, will be presented.
- 2) The incidence of complications will be treated with Kaplan Meier survival analyses. The cumulative incidence curves of these events will be calculated. From these curves, the proportions of these events at 1-3 months, 6 months, 1 year and 2 years will be calculated.

Evaluate the revision rate

- 1) The number of revisions and the number of patients who have had a revision will be presented.
- 2) The incidence of revisions will be treated with Kaplan Meier survival analyses. The cumulative incidence curves of these events will be calculated. From these curves, the proportions of these events at 1-3 months, 6 months, 1 year and 2 years will be calculated.

Evaluate the final explant rate

- 1) The number of definitive explants and the number of patients who have had a definitive explant will be presented.

- 2) The explant incidence will be treated with Kaplan Meier survival analyses. The cumulative incidence curves of these events will be calculated. From these curves, the proportions of these events at 1-3 months, 6 months, 1 year and 2 years will be calculated.

8.3 Comparative analyses

No comparative analysis will be carried out

9 AGREEMENTS CONCERNING DATA PROCESSING

The conventions concerning data processing are detailed in the data handling manual. The main rules are as follows:

- Any variable that is the subject of a queries and not corrected during that queries will retain its original value. A transformation into missing data may be considered for quantitative variables with values outside the limit. This transformation will only take place after validation by the scientific committee during the data review.

9.1 Outliers data

Outliers will be checked. If no correction can be made to these values, they will not be replaced unless otherwise advised by the Scientific Committee when reviewing the data.

9.2 Missing data

In case of missing or partially missing data for the dates, the following rules will be applied:

- Dates
 - If only the day is missing, the day will be considered as equal to the 15th of the month;
 - If only the year is known, the date used for the calculation will be 15/06 of the year in question;
 - If the date is completely missing, it will not be replaced.
- Main endpoint of the study (patients with a primary implantation):
 - Without imputation of missing data: on observations for which EVA information at 1-3 months, 6 months, 1 year and 2 years will be available.
 - With imputation of missing data: these missing values will be replaced by the last known value (LOCF). This imputation method is conservative since the device is expected to decrease the value of EVA.
 - Other methods of extrapolation of some missing data may also be proposed based on the results observed on the first analyses, i.e. extrapolations with replacement of missing values by extreme values or multiple imputation.
 - Other sensitivity analyses will be performed such as multiple imputation or the worst-case scenario for our therapy.

Please explain the rules for box replacements.

No special treatment of missing values is planned for the other variables.

10 APPENDICES

10.1 APPENDIX 1: Calculation of the physical and moral score for SF-12v2 under SAS

The calculation of SF-12v2 scores was described in 2009 by Ware et al.¹

Transformation of Scale Scores

The next step involves transforming each raw scale score to a 0-100 scale using the formula shown below. Table 6.10 provides the information necessary to apply this formula to each scale.

$$\text{Transformed scale} = \left[\frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible raw score range}} \right] * 100$$

This transformation converts the lowest and highest possible scores to zero and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

Table 6.10 Scale Items Aggregated and Range of Possible Scores

SF-12v2 Scale	Sum Final Item Values (after recoding items as in Table 6.1-6.9)	Lowest and highest possible raw scores	Possible raw score range
Physical Functioning (PF)	Items 2a + 2b	2, 6	4
Role Physical (RP)	Items 3a + 3b	2, 10	8
Bodily Pain (BP)	Item 5	1, 5	4
General Health (GH)	Item 1	1, 5	4
Vitality (VT)	Item 6b	1, 5	4
Social Functioning (SF)	Item 7	1, 5	4
Role Emotional (RE)	Items 4a + 4b	2, 10	8
Mental Health (MH)	Items 6a + 6c	2, 10	8

¹ Ware, J.E., Jr., Kosinski, M., Turner-Bowker, D.M., Gandek, B. User's Manual for the SF-12v2® Health Survey With a Supplement Documenting SF-12® Health Survey) Lincoln, RI: QualityMetric Incorporated, 2002 - April 2009 Printing

Step 1: Standardization of Scales (z-scores), Standard Form

First, each SF-12v2 scale is standardized using a z-score transformation using SF-12v2 scale means and *SDs* from the 1998 general U.S. population as given in Table 8.2. A z-score for each scale is computed by subtracting the 1998 general U.S. population mean from each SF-12v2 scale score (0-100 scale) and dividing the difference by the corresponding scale *SD* (0-100 scale) from the 1998 general U.S. population. Note that the SF-12v2 scales scored on the 0-100 scale are used in Step 1. Norm-based SF-12v2 scale

Formulas for z-score standardization of SF-12v2 scales, Standard Form:

$$\begin{aligned}PF_Z &= (PF - 81.18122) / 29.10558 \\RP_Z &= (RP - 80.52856) / 27.13526 \\BP_Z &= (BP - 81.74015) / 24.53019 \\GH_Z &= (GH - 72.19795) / 23.19041 \\VT_Z &= (VT - 55.59090) / 24.84380 \\SF_Z &= (SF - 83.73973) / 24.75775 \\RE_Z &= (RE - 86.41051) / 22.35543 \\MH_Z &= (MH - 70.18217) / 20.50597\end{aligned}$$

Step 2: Aggregation of Scale Scores, Standard Form

After a z-score has been computed for each SF-12v2 scale, the second step involves computation of aggregate scores for the physical and mental summaries using the physical and mental factor score coefficients from the 1990 general U.S. population as given in Table 8.2.

Computation of an aggregate physical summary score consists of multiplying the z-score of each SF-12v2 scale by its respective physical factor score coefficient and summing the eight products, as shown below. Similarly, an aggregate mental summary score is obtained by multiplying the z-score of each SF-12v2 scale by its respective mental factor score coefficient and summing the eight products.

Formulas for aggregating scales in estimating aggregate physical and mental summary scores:

$$\begin{aligned}AGG_PHYS &= (PF_Z * .42402) + (RP_Z * .35119) + (BP_Z * .31754) + \\&\quad (GH_Z * .24954) + (VT_Z * .02877) + (SF_Z * -.00753) + \\&\quad (RE_Z * -.19206) + (MH_Z * -.22069) \\AGG_MENT &= (PF_Z * -.22999) + (RP_Z * -.12329) + (BP_Z * -.09731) + \\&\quad (GH_Z * -.01571) + (VT_Z * .23534) + (SF_Z * .26876) + \\&\quad (RE_Z * .43407) + (MH_Z * .48581)\end{aligned}$$

Step 3: Transformation of Summary Scores, Standard Form

The third step involves transforming the aggregate physical and mental summary scores to the norm-based (50, 10) scoring. This is accomplished by multiplying each aggregate summary score from Step 2 by 10 and adding the resulting product to 50. Formulas are listed below.

Formulas for t-score transformation of summary scores:

Transformed Physical (PCS) = $50 + (\text{AGG_PHYS} * 10)$

Transformed Mental (MCS) = $50 + (\text{AGG_MENT} * 10)$

10.2 APPENDIX 2: CALCULATION AND INTERPRETATION OF THE HAD SCORE^{viii}

Computer System Description Sheet

- "Data Management"

For each item, 4 response modes coded from 0 to 3.

The items of depression (N°1,3,5,5,7,9,11,13) and anxiety (N°2,4,6,8,10,12,14) are alternated. In addition, an alternation in the order of the ratings (from 0 to 3 or from 3 to 0) was performed to avoid the bias associated with their repetition (inverted items).

An overall score is calculated by summing the responses to the 14 items (ranging from 0 to 42), as well as 2 subscores corresponding to the 2 subscales (ranging from 0 to 21).

The higher the scores, the more severe the symptomatology.

The thresholds of the 2 subscores for identifying cases with depressive or anxious symptoms are as follows:

- From 0 to 7: absence of anxiety disorders and depressive disorders
- 8 to 10: suspected anxiety or depressive disorders
- 11 to 21: proven anxiety or depressive disorders

For the overall score, the thresholds are:

- From 0 to 14: no anxiety and depression disorders
- 15 to 42: existence of anxiety and depression disorders

10.3 ANNEX 3: DOCUMENTS REQUIRED FOR THE REVIEW OF DATA

For the review of the data, the following documents must be published:

1. Resolution of queries

- Number of queries published and number of investigators, patients concerned;
- Number and percentages of queries reviewed by the investigator;
- Number of unresolved or uncorrected queries by the investigator (overall analysis and by queries) and number of investigators, patients concerned ;
- Listing of unresolved or uncorrected queries;

2. Investigator population

- Number and percentage of investigators who refused to participate in the study
- Number and percentage of investigators who agreed to participate in the study (with the number and percentage of patients in the study):
 - investigators who included at least 1 patient in the study;
 - investigators who did not include any patients (inactive centers).
- Comparison between participating investigators and centers that refused to participate;

3. patient population

- Patients included in the study;
 - Number of patients included in the study;
 - Number and percentage of patients who completed and returned the self-administered questionnaires;
- Listing of patients who did not meet the inclusion criteria;
- Listing of patients for whom the indication for treatment is missing;
- Number and percentage of retrospective patients in the study (primary implanted patients without a pre-test phase self-test questionnaire)
- Descriptive statistics of all variables (medical inclusion questionnaire, follow-up and self-administered medical questionnaires, complication sheets), including derived variables, with the percentage of missing data, to obtain distributions of the variables;

4. Non-inclusion register

- Number of patients in the non-inclusion register
- Descriptive statistics of all variables

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